Pharmacokinetic and pharmacodynamic profile of maraviroc in rhesus macaques after a single oral dose

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Maraviroc for pre-exposure prophylaxis

- FDA-approved

- Very potent, functional CCR5 antagonist (EC$_{50}$ = 0.1-4 nM)

- Active against NRTI, NNRTI, PI, and enfuvirtide-resistant viruses

- Concentrates in rectal and vaginal secretions after oral dosing in humans (JID 2011, JAIDS 2009)

- Phase II study of safety, tolerability, and adherence of MVC, MVC+FTC or Truvada for PrEP among MSM in development (HPTN 069)

- Prophylactic efficacy of oral MVC not evaluated in animal models
Objective

To evaluate the PK profile of MVC in rhesus macaques and relate drug levels with PrEP efficacy

- Define human-equivalent doses of MVC in macaques
- Evaluate MVC penetration in rectal and vaginal tissues
- Relate MVC exposure with CCR5 occupancy and inhibition of virus replication
- Evaluate efficacy of MVC in preventing transmission in a macaque model of HIV infection
Single dose pharmacokinetic study

- Indian rhesus macaques (9 females, 3 males)

- MVC (44 mg/kg) given orally by gavage

- Blood, rectal, and vaginal secretions collected at 2h, 5h, 24h, 2d, 4d, and 7d. Secretions collected in wicks (Weck-Cel Surgical Spear)

- MVC measured by HPLC-MS/MS with a LOQ of 5 ng/ml

- Half-life of MVC bound to CCR5 calculated using a MIP-1β internalization assay
Pharmacokinetic profile of maraviroc in plasma, vaginal, and rectal secretions after a single oral dose

![Graph showing the pharmacokinetic profile of maraviroc in plasma, vaginal, and rectal secretions.](image-url)
Maraviroc pharmacokinetic parameters in plasma after a single oral dose of 44 mg/kg

<table>
<thead>
<tr>
<th>Animal ID</th>
<th>AUC$_{0-24h}$</th>
<th>Tmax</th>
<th>Cmax</th>
</tr>
</thead>
<tbody>
<tr>
<td>01D431</td>
<td>307</td>
<td>2</td>
<td>29</td>
</tr>
<tr>
<td>01D478</td>
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<td></td>
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<tr>
<td>01D520</td>
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<td>97D219</td>
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<td>9969</td>
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<td>A2E027</td>
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<td>A3E021</td>
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<td>AL87</td>
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</tr>
<tr>
<td>AM43</td>
<td>1220</td>
<td>2</td>
<td>711</td>
</tr>
<tr>
<td>RH6635</td>
<td>7540</td>
<td>2</td>
<td>603</td>
</tr>
<tr>
<td><strong>Median</strong></td>
<td><strong>1,685</strong></td>
<td><strong>2</strong></td>
<td><strong>451</strong></td>
</tr>
</tbody>
</table>

**Table 2. PK Parameters and AUC$_{0-24h}$ Ratios for Maraviroc in BP, CVF, and VT**

Data presented as median (interquartile range) for C$_{max}$, AUC$_{0-24h}$, and AUC ratios; Tmax is presented as median (range); VT C$_{max}$ units are nanograms per gram and AUC units are ng·h/g.
Pharmacokinetic parameters of MVC in plasma, rectal, and vaginal secretions after a single oral dose

<table>
<thead>
<tr>
<th>PK parameters</th>
<th>Blood plasma</th>
<th>Rectal secretions</th>
<th>Vaginal secretions</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{AUC}_{0-24h}$, (ng*h/ml)</td>
<td>1,685</td>
<td>12,720</td>
<td>11,910</td>
</tr>
<tr>
<td>$T_{\text{max}}$, (h)</td>
<td>2</td>
<td>24</td>
<td>5</td>
</tr>
<tr>
<td>$C_{\text{max}}$, (ng/ml)</td>
<td>451</td>
<td>2,329</td>
<td>991</td>
</tr>
</tbody>
</table>
What about CCR5-bound maraviroc?
Analysis of MVC binding to CCR5 using a co-receptor occupancy assay

Presented at the 6th Int. Workshop on HIV Transmission, 14 – 15 July 2011, Rome, Italy
CCR5 occupancy at different concentrations of MVC

Log$_{10}$ maraviroc concentration | Receptor occupancy

-10.0 -7.5 -5.0 -2.5 0.0 2.5

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CCR5 internalization by MIP1β in Rhesus PBMCs prior to oral MVC dosing

- PBMCs: 19.04%
- +MIP1β: 5.69%
- +MVC: 17.38%
- +MVC +MIP1β: 16.94%
CCR5 internalization in Rhesus PBMCs after a single oral dose of MVC

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<table>
<thead>
<tr>
<th>Time</th>
<th>No MIP1β</th>
<th>+ MIP1β</th>
</tr>
</thead>
<tbody>
<tr>
<td>t = 2 hr</td>
<td>22.96%</td>
<td>22.43%</td>
</tr>
<tr>
<td>t = 24 hr</td>
<td>21.76%</td>
<td>19.91%</td>
</tr>
<tr>
<td>t = 48 hr</td>
<td>22.06%</td>
<td>13.3%</td>
</tr>
<tr>
<td>t = 7 days</td>
<td>21.25%</td>
<td>5.95%</td>
</tr>
</tbody>
</table>
Half-life of MVC bound to CCR5 in macaque PBMCs after a single oral dose

$\tau_{1/2} \sim 2$ days
Pharmacodynamic profile of MVC

Relationship between MVC concentrations, CCR5 occupancy, and virus replication established *in vitro*

- CD8-depleted rhesus PBMCs exposed to an R5-tropic SHIV$_{162P3}$ isolate in the presence of different concentrations of MVC

- Occupancy of CCR5 measured by a MIP1β internalization assay

- Infection outcome evaluated after 4-7 days of culture by quantitative analysis of viral expression (RNA and DNA)
Relationship between inhibition of virus replication by MVC and CCR5 occupancy

**IC$_{50}$** = 1.5 - 4.6 nM (0.8-2.3 ng/ml) for RNA replication.

**IC$_{50}$** = 3.9 - 5.7 nM (2-2.9 ng/ml) for DNA replication.

**IC$_{50}$** = 0.7 nM (0.37 ng/ml) for receptor occupancy.

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MVC concentrations in rectal secretions at 2-3 days are associated with maximum CCR5 occupancy and protection from infection in rhesus PBMCs.
Summary

- A single dose of 44 mg/kg of MVC given orally to rhesus macaques results in MVC levels in plasma comparable to those seen in humans receiving 300 mg.

- As in humans, MVC concentrates in rectal and vaginal tissues after oral dosing, suggesting that rhesus macaques may be a suitable species for preclinical evaluation of PrEP efficacy of MVC.

- Long MVC persistence in rectal secretions provides an added advantage for PrEP against rectal transmission.

- MVC concentrations in rectal secretions at 2-3 days exceed the EC_{90-99} and associate with 100% receptor occupancy.
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